REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

A. Overview of the Invention and Newly Added Claims.

The invention provides means for ameliorating the effects of the aging process on the brain.[1] The invention further provides means for influencing terminal axonal density in a region of the brain remote from, but innervated by, neurons in another region of the brain.

In particular, the present disclosure teaches one of ordinary skill in the art to select targeted cell populations in the aging brain that are receptive to a neurotrophin delivered according to the invention; e.g., the cholinergic forebrain, the cortex (any region), the enthorhinal cortex, the substantial nigra, and motor neurons. Specification at page 7, lines 11-19. Once the targeted region has been selected, "delivery sites are selected for stereotaxic distribution so each unit dosage of growth factor composition is delivered into the brain at the target site [*inter*regional delivery], or within diffusion reach of a chemotropic (concentration) gradient leading to the target site [*intra*regional delivery]." Specification at page 7, lines 25-30, and Example IV.

More particularly, *intra*regional delivery of growth factors targets nearby neuronal populations; i.e., those within a chemotropic gradient distance of the growth factor delivery sites. The inventor was the first to demonstrate that such treatment is effective in animals as they age, even in the absence of damage, disease or defect within the neuronal population treated.

[1] The term "normal" aging has been deleted from the claims as being potentially ambiguous with respect to the meaning of "normal" in this context.

*Inter*regional delivery of growth factors targets neuronal populations within a *non-*chemotropic distance of the delivery sites; i.e., populations that reside in a different region of the brain. In this respect, the inventor again was the first to demonstrate that aging in the primate brain is associated with a significant reduction in cholinergic innervation not only of the forebrain, but also of the **cortex** (Specification at page 5, lines 7-9). The invention provides the first demonstration that such atrophy within more than one region of the brain can be reversed through delivery of nerve growth factors to even a single region of the brain.

This phenomenon is especially well demonstrated in Example IV herein, wherein *in vivo* delivery of a neurotrophin expressing vector into the forebrain influenced growth in terminal axons within the cortex. *See also,* Specification at page 7, lines 1-25 (the influence of expressed neurotrophins on distant regions of the brain is a non-chemotropic phenomenon, possibly involving downstream activation of signaling pathways).

Claim 1 and its dependent claims 2-16 extend to both *intra-* and *inter-* regional delivery of growth factors. Newly added Claims 17-20 are directed in particular to *inter*regional delivery methods. No new matter is added to the application by the inclusion of Claims 17-20 therein. Entry of the new claims is therefore requested.

B. Substitute Specification Pages.

In the specification, the preliminary amendment of April 16, 2001 deleted paragraphs on pages 3 and 4 to remove all references to Figures 1, 2 and 3(A) through (D) therefrom. The figure formerly designated as Figure 3(D) was amended to be identified instead as Figure 1, and the specification was amended accordingly. The figure formerly designated as Figure 4 was amended to be identified instead as Figure 2, and the specification was amended accordingly. No new matter was added to the application by virtue of these earlier amendments.

The present Office Action requests that Applicant submit substitute page(s) reflecting the amendments to pages 3 and 4 of the specification. A substitute page 3 is therefore enclosed, entry of which is requested.

C. Response to Objection to Priority Claim.

In the Office Action, Applicant's priority claim to Serial No 09/060,543, now U.S. Patent No. 6,451,306 (the '306 Patent) is refused on the asserted basis that the parent application "fails to disclose a method for ameliorating neuronal atrophy and loss accompanying normal aging in the mammalian brain by delivering a transgene encoding a growth factor to preselected sites in the brain." Applicant respectfully traverses the refusal of the priority claim on the basis that (a) Applicant is entitled to the priority of the parent application for all subject matter common to it and the present application; and (b) the claimed subject matter is found in the parent application.

In the first respect, Applicant notes that the present application is designated as a continuation-in-part of the parent application. Under 35 USC Section 120, continuation-in-part applications are entitled to the benefit of the filing date of an earlier application if there is at least one common inventor between the applications, the CIP was filed while the parent application was still pending, and the CIP contains a reference back to the parent application. *See*, MPEP 201.08. All of these conditions are met in the present application, which is therefore entitled to claim the priority of the parent application. On this basis alone, the refusal to grant Applicant's priority claim for subject matter common to the present application and its parent should be withdrawn.

Secondly, presently claimed subject matter may be found in the disclosure of the parent application as set forth in the Table below:

LIMITATIONS OF PRESENT CLAIM 1	DISCLOSURE OF PARENT APPLICATION 09/060,543 (US Patent No. 6,451,306)
A method for ameliorating neuronal atrophy and loss accompanying normal aging in the mammalian brain,	*See, e.g.,* Specification at page 2, lines 6-12: delivery of recombinant nerve growth factors into the mammalian brain; invention is capable of stimulating neuronal growth and recovery of function, and can be used for therapy of defective, diseased or damaged cells in the brain. *See also*, Example IV: ex vivo method practiced in aged primates, followed by reversal of age-related neuronal loss.
the method comprising delivering a unit dosage of a growth factor-encoding transgene composition to preselected delivery sites in the brain,	*See*, regarding "unit dosage": Specification at page 3, lines 1-6). *See also*, regarding "growth factor-encoding transgenes": Specification at page 7, lines 10-21 (growth factors); at page 11, line 11 through page 13, line 3 (vectors encoding transgenes); and at page 19, line 5 through page 21, line 20 (e.g., "compositions of neurotrophin encoding transgenes" at page 19, line 6). Additionally, *see,* regarding delivery to preselected delivery sites in the brain: Specification at page 22, line 1 through page 23, line 6), and Example III.
Wherein the encoded growth factor is expressed in the brain, and stimulates axonal growth in targeted growth factor-receptive neurons therein.	*See,* regarding expression in the brain: Examples IV and V. *See* regarding stimulation of growth: Specification at page 2, lines 6-9, and Example IV.

The disclosure of the parent '306 Patent teaches therapeutic methods for delivery of growth factor encoding transgenes to the brain via an indirect (*ex vivo* via a host cell) route of administration. Claims 1-4, 6, 9 and 11-20 of the present application extend to such a method of treatment as applied to the aging brain. In that respect, therefore, these claims are clearly entitled to the full benefit of the priority of the parent '306 Patent.

Claims 1, 5, 7 and 8 also extend to *in vivo* treatment. The practice of *in vivo* therapy is less explicitly described in the disclosure of parent '306 Patent, but is unambiguously supported by the disclosure of an intervening child application, Serial No. 09/620,174, filed July 19, 2000, now US Patent No. 6,683,058 (the '058 Patent). In accord with MPEP Section 201.11, Applicant has amended the specification to further claim the priority of the child '058 Patent, to which Claims 1, 5, 7 and 8 are fully entitled.

Indeed, the Examiner is apparently in agreement in this respect, in that in that the present claims are rejected as "double patenting" of the invention claimed in the child application, now U.S. Patent No. 6,683,058, and characterized as encompassing "the same invention and obvious variants thereof." As such, Claims 1, 5, 7 and 8 are at least entitled to the priority of the filing date of the child application; i.e. July 19, 2000, if not also the benefit of the parent's filing date of April 15, 1998.

Based on the foregoing, reconsideration and withdrawal of the refusal to grant Applicant's priority claim is therefore requested.

D. Response to Double Patenting Rejection.

With respect to the rejection of Claims 1-3, 5, 7, 8 and 11-15 on the basis of obviousness-type double patenting, Applicant submits a terminal disclaimer with respect to the patent on which the rejection is based; i.e., US Patent No. 6,683,058. This submission should not be considered to be acquiescence in the merits of the rejection, which is disputed on the basis that neither the efficacy of the presently claimed invention for treatment in response to the process of

aging, nor the invention's utility for treatment of one region of the brain to benefit another, are claimed in the '058 Patent. Applicant therefore submits that the present invention is not obvious over the claimed invention of the '058 Patent. Thus, the terminal disclaimer submitted herewith is provided solely for the purpose of expediting allowance of the claims in question.

For the same reasons, Claims 1-3, 5, 7, 8 and 11-15 are not obvious in view of the claims of co-pending Patent Application Serial No. 10/032,952. In particular, neither the efficacy of the presently claimed invention for treatment in response to the process of aging, nor the invention's utility for treatment of one region of the brain to benefit another, are claimed in the '952 Application. Applicant therefore submits that the present invention is not obvious over the claimed invention of the '952 Application, and so the obviousness-type double patenting rejection based thereon should be withdrawn.

Further with respect to the provisional obviousness-type double patenting rejection based on the '952 Application, Applicant notes that the '952 Application has a later filing date than the present application; i.e., the present application was filed on 12/5/2000, while the application on which the rejection is based was filed on 10/26/2001. As such, whenever issued, a patent based on the latter application will necessarily expire *after* the expiration in due course of a patent based on the present application.

Thus, while a double patenting rejection could be procedurally appropriate in the latter application, it is not properly raised in the present application. Applicant therefore submits that the double patenting rejection stated should be withdrawn in this, the earlier filed application, at the time required by the procedure set forth in MPEP Section 804(I)(B).

E. Response to Rejection of Claims 1-5, 7, 8 and 11-15 under Section 112, First Paragraph.

The claims have been rejected as lacking enablement with respect to the delivery into the brain of "any growth factor encoding transgene in any vector via various administration routes." Office Action at page 7. However, Applicant respectfully notes that claims to different

applications of the same method, having scope similar to that of present Claim 1, were allowed and issued by this same Examiner in the priority applications that matured into US Patent No. 6,451,306 (*ex vivo* delivery: any transgene in any vector delivered via grafting of host cells) and US Patent No. 6,683,058 (*in vivo* delivery: any transgene in any vector delivered directly to the brain by various routes of administration).

With respect to enablement of successful *in vivo* and *ex vivo* delivery of nerve growth factors into the brain, the present disclosure is comparable in content and scope to the disclosures of the clearly enabling parent and child applications. To more clearly draw a parallel between the scope of the present claims and those already issued in the priority '306 and '058 Patents, the present "route of administration" claims (Claims 1, 5 and 6) have been amended with respect to the route of administration limitations to specify that administration may be accomplished "directly" (by *in vivo* means similar to those claimed in the '058 Patent) or "indirectly" (by *ex vivo* means similar to those claimed in the '306 Patent).

Based on the foregoing, Applicant submits that the rejection of the claims under Section 112, first paragraph, should clearly be withdrawn on the same basis that the Examiner withdrew similar rejections of claims in the applications for the parent '306 Patent and child '058 Patent. Therefore, reconsideration and withdrawal of the rejection of the claims under Section 112, first paragraph is respectfully requested.

F. Response to Rejection of Claims 1-5, 7, 8 and 11-15 Under Section 102(b) Based on Mandel.

The claims are rejected as being anticipated by Mandel, *et al.*, 1999 (Mandel). Applicant respectfully traverses the rejection.

Mandel neither teaches nor suggests the claimed invention. The Mandel paper discusses the results of an experiment in which an AAV vector encoding NGF was injected into two sites in the lesioned brains of rats, after which damaged cells within the lesion were observed to

survive in greater numbers than in lesioned, untreated brains. Mandel, at page 60, column 2 through page 61.

Mandel's observation that cell survival within a lesion can be supported with NGF in no way suggests whether or how NGF expression will impact neuronal populations or axonal termini at *any* point outside of the lesion. Indeed, success in supporting the survival of an existing but damaged cell does not suggest that growth of new neurons or axonal termini of neurons can be stimulated at all, whether within or outside of the lesion.

At most, therefore, Mandel suggests that one might *experiment* with NGF to determine if cell survival can be enhanced within damaged portions of the brain. But Mandel fails to provide the art with any reason to expect, or even imagine, that the goals achieved by the invention could be reached by delivery of NGF to the brain. In particular, nothing in Mandel suggests in any way that the processes of aging can in any way be impacted by delivery of NGF to the brain. And Mandel most certainly does not suggest that delivery of NGF to one region of the brain could have any impact at all on other regions of the brain.

In this respect, one discovery underlying the presently claimed invention is that expression of nerve growth factors in one region of the brain can have profound effects on growth of axonal termini in *remote* parts of the brain. For example, as stated in the Specification with respect to results obtained from the practice of one embodiment of the invention in primates:

> "[the] effects of cellularly-delivered NGF of cortical cholinergic innervation were exerted at a distance, since the growth factor was presented to the cholinergic soma yet influenced terminal axon density in the distant cortex. Remarkably, reversal of age-related axonal attenuation in both the soma and the cortex was achieved after only three months of NGF delivery to the primate brain soma. Thus, practice of the invention significantly and efficiently ameliorates neuronal loss accompanying the normal aging process in the primate brain." *Specification*, at page 6, lines 24-30.

As confirmed in Example IV of the Specification, these remarkable results were achieved by administration of nerve growth factor-encoding transgenes to sites in the brain selected for the even distribution of the delivery sites across the rostral-caudal distance of the forebrain, and to target a neuron-rich region of the cholinergic soma. Specification at page 16, line 25 through page 17, line 5. Remote regions of the brain that are heavily innervated by neurons from the cholinergic region of the brain treated experienced substantial increases in terminal axonal density (the temporal and insular cortices), but areas of lesser cholinergic innervation enjoyed an increase in axonal density as well (the cingulated and frontal cortex, as well as the hippocampus). Specification at page 20, lines 1-10.

Clearly, therefore, the invention has established that a neurotrophin expressed in one site of the brain may influence axonal growth in distant neuronal populations that are (a) innervated by neurons from the region of the brain containing the delivery sites; and (b) receptive to the neurotrophin. Such potentially receptive neuronal populations can be readily identified, given knowledge in the art of the distribution and binding characteristics of neurotrophin receptors in the brain. For example, *see,* Ebendal, *J.Neurosci.Rsch.*, 32:461-470 (1992)(review paper regarding previous work in the art providing an overview of the relatively widespread distribution of trk receptors for NGF family neurotrophins throughout the brain); Sariola and Saarma, *J.Cell Sci.,* 116:3855-3862 (2003)(activity of GDNF family neurotrophin and distribution of receptors therefor in the brain). Copies of the cited papers are of record in the child priority application—additional copies will be provided if needed.

All of the foregoing teachings of the present disclosure are completely absent from Mandel. As such, Mandel clearly does not anticipate the presently claimed invention. Reconsideration and withdrawal of the rejection of claims under Section 102(b) based on Mandel is therefore respectfully requested.

G. Response to Rejection of Claims 1-5, 7, 8 and 11-15 Under Section 102(b) Based on Felgner.

Felgner (US Patent No. 5,580,859) has an extensive prosecution history from which it can be readily confirmed by the Examiner that the disclosure was considered as enabling only a fraction of the embodiments mentioned. In particular, the disclosure was found only to be enabling for the introduction of "naked" polynucleotides into muscle (see, e.g., Felgner at Claim 1).

It is axiomatic that, to serve as an anticipating reference, the reference must enable that which it is asserted to anticipate: "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003). *See also, Bristol-Myers Squibb v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1374, 58 USPQ2d 1508, 1512 (Fed. Cir. 2001) ("To anticipate the reference must also enable one of skill in the art to make and use the claimed invention.") and, *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter.").

Therefore, given the lack of an enabling disclosure in Felgner for therapeutic methods of introducing of polynucleotides into the brain, the reference cannot be relied upon as an anticipating reference against later claims to such methods. As such, the record fails to make a *prima facie* case for anticipation of the present claims on the basis of the Felgner reference.

Furthermore, notwithstanding the relative merits of Felgner's mention of introducing polynucleotides into the brain in any context, it is clear that Felgner neither teaches nor suggests numerous aspects of the presently claimed invention.

Nothing in the reference provides the art with any reason to expect, or even imagine, that the goals achieved by the invention could be reached by delivery of NGF to the brain. Felgner's mention of introducing polynucleotides into the medial septum of the brain does not provide one with any guidance regarding how to accomplish the delivery, beyond a suggestion that polynucleotides be "targeted" to cholinergic neurons by a single injection into the medial septum. Felgner, Col. 16, lines 5-12. Even then, Felgner does not provide one with any basis upon which to determine whether or how expression of the encoded protein will impact neuronal populations or axonal termini at any point beyond the injection site.

In addition, nothing in Felgner suggests in any way that the processes of normal aging can in any way be impacted by delivery of NGF to the brain. And Felgner most certainly does not suggest that delivery of NGF to one region of the brain could have any impact at all on other regions of the brain.

In short, Felgner does not anticipate the presently claimed invention obvious. Reconsideration and withdrawal of the rejection of claims under Section 102(b) based on Felgner is therefore respectfully requested.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date June 21, 2004

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Enclosures: Terminal Disclaimer
Substitute Page 3

BRIEF DESCRIPTION OF THE DRAWINGS

[Figure 1: NGF-Secreting and Control Grafts Within the Intermediate Component of the Ch4 region.

(A) p75-immunolabeled coronal section of the intermediate component of Ch4 showing an NGF-secreting cell graft. The graft is penetrated by cholinergic axons. **(B)** Thionin-stained section taken adjacent to that in (A) identifies graft boundaries within the Ch4 region. **(C,D)** Comparable p75-immunolabeled and thionin-stained sections from a control aged monkey that received ß-gal expressing fibroblasts. Graft survival is comparable to that of NGF grafts, but fewer axons penetrated the grafts. Scale bar = 1 mm.

Figure 2: Quantification of Cholinergic Innervation Densities.

Cholinergic axon density was determined in multiple cortical regions. Quantified regions included inferior temporal cortex layers II (**IT-II**) and V (**IT-V**); Insular cortex layers II (**INS-II**) and V (**INS-V**); cingulate cortex layer II (**CING**); frontal cortex layer II (**FR**); and hippocampal formation, stratum radiatum of CA1 (**HF**). Axon densities were determined by superimposing a 6 X 6 grid over a highly magnified image captured from one of the defined regions (see inset). All AChE-stained fibers crossing the gridlines (arrows in inset) were counted to yield an index of innervation density. Scale bar = 5 mm. Bar in inset = 35 μm.

Figure 3: Age-Related Decline in Mean Cortical Cholinergic Innervation is Reversed by NGF Gene Delivery to Cholinergic Somata in the Basal Forebrain.

AChE staining in the insular cortex of young, aged-control, and aged-NGF-grafted rhesus monkeys. **(A)** The normal density of cholinergic axons is illustrated in young subjects. **(B)** Axon density is reduced in aged, control-grafted subjects. **(C)** AChE-stained fiber density is significantly increased in aged monkeys that received grafts of autologous NGF-secreting fibroblasts into the intermediate division of Ch4. Scale bar A - C = 35 μm. **(D)]** --Figure 1:-- Quantification of cholinergic axon density. To compare cholinergic innervation densities across multiple cortical regions, normalized z-scores of density measurements from each cortical region were calculated and then averaged. A significant overall group effect was present by one way ANOVA ($p < 0.0001$). Aging was

associated with a significant reduction in overall cholinergic fiber density (* $p < 0.0001$, Post hoc Fischer's), and this was restored in recipients of NGF-secreting cells. Black bars, young monkeys; red bars, aged-controls; blue bars, aged-NGF-grafted subjects. Error bars represent standard errors of the mean.

[Figure 4:] --Figure 2:-- Changes in Cholinergic Axon Density Across Cortical Regions.

Control-aged monkeys (red bars) exhibit a significant decline in cortical cholinergic innervation compared to young intact animals (black bars) in most cortical regions. Aged recipients of NGF-secreting grafts (blue bars) exhibit a significant reversal of age-related loss in cholinergic innervation; however, this effect is significant only in cortical regions (insula and inferior temporal cortex) innervated primarily by cholinergic neurons of the intermediate division of Ch4, which was targeted for grafting. Numbers in parentheses below each cortical region indicate p value for ANOVA.

LEGEND TO FIGURES 1-[4:] --2:--

* - significantly reduced compared to young animals ($p < 0.05$, Post hoc Fischer's);

[# - significantly increased compared to aged control animals ($p < 0.05$, Post hoc Fischer's). INS: insular cortex; IT: inferior temporal cortex; CING: cingulate cortex; FR: frontal cortex; HF: hippocampal formation.

Figure 5:

Reprint of the nucleotide sequence coding for human beta nerve growth factor as shown in GENBANK Accession No. X52599.

Figure 6:

Reprint of the nucleotide sequence coding for human NT-3 as shown in GENBANK Accession No. E07844.]

Figure 1: Quantification of cholinergic axon density. To compare cholinergic innervation densities across multiple cortical regions, normalized z-scores of density measurements from each cortical region were calculated and then averaged. A significant overall group effect was present by one way ANOVA ($p < 0.0001$). Aging was associated with a significant reduction in overall cholinergic fiber density (* $p < 0.0001$, Post hoc Fischer's), and this was restored in recipients of NGF-secreting cells. Black bars, young monkeys; red bars, aged-controls; blue bars, aged-NGF-grafted subjects. Error bars represent standard errors of the mean.

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LEGEND TO FIGURES 1-2:

* - significantly reduced compared to young animals ($p < 0.05$, Post hoc Fischer's);